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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/666,430	09/21/2000	Delphine Gabrielle Josette Rea	4205.1US	6289
24247	7590	07/26/2005	EXAMINER	
TRASK BRITT P.O. BOX 2550 SALT LAKE CITY, UT 84110			EWOLDT, GERALD R	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/666,430

**Applicant(s)**

REA ET AL.

**Examiner**

G. R. Ewoldt, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 27 April 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 and 40-81 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 40-81 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
    Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
    Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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#### DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 4/27/05 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks, filed 4/27/05, have been entered.

2. Claims 1, 40-68, and newly added Claims 69-81, are being acted upon.

3. Applicant is advised that the substitute specification filed 3/18/03 has been entered.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 40-68, and newly added Claims 69-81 stand/are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

the *in vitro* induction of non-responsiveness of MHC-matched clonal T cells to a defined antigen when dexamethasone-treated dendritic cells (DCs) have been loaded with the same defined antigen,

does not reasonably provide enablement for, *in vivo* or *in vitro* induction of non-responsiveness of polyclonal T cells to any undefined antigen or the *in vivo* induction of non-responsiveness when an "unwanted T-cell response" is ongoing, for the reasons of record as set forth in papers mailed 6/29/01, 9/19/02, 5/21/03, and 12/27/04.

As set forth previously, The Examiner's position is simply that the data disclosed in the instant specification (and newly provided 1.132 declaration) provides insufficient support for the method of the instant claims. *In vivo* data is not required, however, an enabling specification is required.

Neither the single relevant example of the specification (Example 4), nor the newly provided data of the Inventor's 1.132 declaration, actually address the invention of the instant claims. Example 4 merely discloses that a T cell response to

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a known antigen can be reduced employing a known immunosuppressive drug (Dex). The Inventor's declaration provides little additional enablement for the claimed method. Example 1 teaches that an *in vitro* alloimmune T cell response (MLR) can be suppressed employing Dex-treated DC. Example 2 teaches that a long term cultured Dex-treated DC (not a cell that could be employed for *in vivo* treatment) could reduce an allo-response.

The examples fail to demonstrate how the antigens associated with the unknown T cell responses are established and employed to reduce an unwanted T cell response. Note that the example of the specification discloses only a known antigen that is not associated with any known unwanted T cell response, and the examples of the declaration are not antigen specific - alloimmune responses are not considered to be antigen-specific responses. Regarding the assertion that the DCs in the example present the same antigens as the skin graft cells, Applicant provides no evidence of this and no evidence that an antigen-specific unwanted T cell response is reduced. Regarding Hancock et al. 1996, the reference teaches the importance of CD40-CD40L interactions in allograft rejection. Applicant's assertions as to the "presumptions" of the authors (regarding alloantigens) comprises nothing more than an attorney's assertion which is not found to be convincing. Accordingly, the submissions of record comprise insufficient support for a method comprising the reduction of an unwanted antigen-specific T cell response.

Probably the most well-studied of the presumed pathogenic autoantigens is MBP. MBP-reactive T cells from MS patients have been isolated, and methods for both inducing T cell tolerance to MBP and reducing the number of said cells have been tried. Neither method provided an effective treatment for the disease (see Marketletter, 1999 and Zhang et al. 2002). Note that in Zhang et al. it is established that the number of MBP-reactive T cells has been reduced (Figure 1), but even the authors' tortured evaluation of data leaves them with the finding that while depletion of said cells might initially "coincide" with "slow progression", disease progression "seemed to accelerate" after 12 months.

Thus, it remains the Examiner's position that the specification fails to adequately describe how to make and use the method for producing antigen-specific tolerized T cells for the reduction of unwanted T cell responses as set forth in the instant claims.

Applicant's arguments, filed 4/27/05, have been fully considered but they are not persuasive. Applicant argues, that the previous 1.132 declaration of Inventor Offringa states that alternatively activated DC can be used to modulate alloimmune responses. Applicant then discusses transplant rejection based on differences in HLA antigens.

It remains the Examiner's position that the declaration of Inventor Offringa, and Applicant's arguments, address different methods than those of the instant claims. The method of the instant claims encompasses the reduction or tolerization of an antigen-specific T cell response. Alloimmune responses are not considered antigen-specific as the term is generally used in the immunological arts. Note that allogeneic MHC antigens stimulate an immune response *without being processed into peptides* as is required for other antigen-specific responses. Additionally, MHC molecules are recognized on both allogeneic and self APCs

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(see *Fundamental Immunology*, Paul, ed., 1999). Thus, an allogeneic system, as used to demonstrate efficacy here, is insufficient for the claimed method involving antigen-specific immunosuppression of tolerization.

Applicant argues that the ordinarily skilled artisan would know how to load DCs with antigens without having to determine the identity of each antigen and cites "A.K. Abbas at 319-320".

Applicant is advised that there is no Abbas reference of record. Applicant has improperly submitted an Abbas reference, however, the reference comprises no pages 319 or 320.

Applicant again cites Greten et al., Stemme et al., and Nicholson et al., and Zhang et al. (previously cited by the Examiner).

It remains the Examiner's position that: 1) Greten et al. does not establish any particular pathogenic HTLV-1 molecule, nor that elimination of any particular T cells would efficaciously treat HTLV-1 disease, 2) Stemme et al. merely identifies a "potentially significant" molecule, 3) Nicholson et al. speculates that heteroclitic APLs "may have a role in the initiation of autoimmunity", and 4) Zhang et al. teaches that deletion of certain potentially pathogenic T cells may actually accelerate disease.

Regarding the breadth of the claims, all experiments have been performed employing dexamethasone (Dex) exclusively. It is noted, however, that only Claims 50, 54, 57, 60, 64, 67, and 69-81 are limited to this glucocorticoid. Indeed, not all the claims even recite the use of a glucocorticoid; it is unclear how the instant specification can possibly be enabled for those claims. And, it is noted that Applicant's own submission, *Glucocorticoids* from Stanford's HOPES project, teaches that not all glucocorticoids comprise the same biological activities. Dex is described as having more anti-inflammatory activity than prednisone or hydrocortisone, and hydrocortisone is described as having more undesirable activity than either Dex or prednisone. The teaching echoes what has been well-known in the art for some time, i.e., that glucocorticoids comprise different biological activities in different contexts, see for example Bray et al. (1978).

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Finally, it is noted that no nexus has been established between a reduction in IL12p40 production and a reduction in an unwanted T cell response, in the generic method of Claim 1. The specification discloses a single example in which IL12p40 production is stimulated in a single way and, assertedly, reduced, again, in just a single way. As no cause-and-effect has been tested for, and thus, not established, it is just as, or more, likely that the reduction of IL12p40 is just an artifact, or at most a marker for the reduction of an antigen-specific T cell response.

6. Claims 1, 46, and 55 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, there is insufficient written description to show that Applicant was in possession of "means for reducing IL-12p40 production by said dendritic cell" or "means for causing said dendritic cell to secrete IL-10 in vitro", other than dexamethasone. As said "means" comprise an unknown genus of indeterminate size, one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus.

Applicant's arguments, filed 4/27/05, have been fully considered but they are not persuasive. Applicant again cites 35 U.S.C. 112, paragraph six.

Applicant is again advised that no rejection under 35 U.S.C. 112, paragraph six has been made.

Applicant argues that Dex is a sufficiently representative example of glucocorticoids.

It remains the Examiner's position that Dex is not a sufficiently representative number of means for reducing IL-12p40 production by a dendritic cell or means for causing a dendritic cell to secrete IL-10 in vitro.

7. Claims 40-68 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at

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the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A substance capable of activating a glucocorticoid receptor (Claims 40 and 51-55)

B) A method for preparing an isolated dendritic cell, said method comprising: isolating peripheral blood monocytes from a subject; culturing the peripheral blood monocytes to differentiate into dendritic cells; activating the dendritic cells with a glucocorticoid; loading the dendritic cells with an antigen; and isolating said loaded, activated dendritic cells (Claim 56).

C) The method according to claim 56, wherein the antigen comprises an allogeneic antigen (Claim 59).

D) A method for obtaining a dendritic cell capable of tolerizing a T-cell or tolerizing a T-cell in a graft or transplant recipient (Claims 64 and 65).

Regarding A) the specification supports binding but not activating.

Regarding B) the specification does not disclose this generic method for preparing any type of isolated DC.

Regarding C) the specification does not disclose the generically-claimed method employing a generic allogeneic antigen.

Regarding D) the specification discloses only tolerizing T cells to an antigen and not tolerizing a generic T-cell or tolerizing a T-cell in a graft or transplant recipient.

Applicant's arguments, filed 4/27/05, have been fully considered but they are not persuasive.

Regarding A), Applicant cites paragraph 18 of the specification.

Paragraph 18 discloses a glucocorticoid hormone for activating DCs and not a substance for activating a glucocorticoid receptor.

Regarding B), Applicant cites paragraphs 18, 24, and 35 of the specification.

The cited paragraphs do not disclose the limitations of the claims, e.g., the preparation of a generic isolated DC employing a peripheral blood monocyte.

Regarding C), Applicant cites paragraphs 18 and 35 of the specification.

The cited paragraphs do not disclose the limitations of the claim, e.g., the preparation of a generic isolated DC employing a peripheral blood monocyte and an allogeneic antigen. Note

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that paragraph 35 does disclose an alloantigen, but the disclosure is made in a specific example and cannot support a generic method.

Regarding D), Applicant cites paragraphs 18 and 22 of the specification.

The cited paragraphs do not disclose the limitations of the claims, e.g., tolerizing a T-cell or tolerizing a T-cell in a graft or transplant recipient. Note that paragraphs 18 and 22 disclose methods employing a glucocorticoid hormone and not Dex (Claim 64) or anything (Claim 65).

8. The following are new grounds for rejection.

9. Claims 69-81 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method for preparing a pharmaceutical composition for reducing an unwanted T-cell response to an antigen in a host, said method comprising:

culturing peripheral blood monocytes from said host to differentiate into dendritic cells *in vitro*;

contacting said dendritic cells *in vitro* with an antigen against which said T-cell response is to be reduced, thereby loading said dendritic cells with the antigen;

contacting said dendritic cells with dexamethasone; activating the CD40 receptor on said dendritic cells; and forming a pharmaceutical composition comprising said loaded, activated dendritic cells. (Claim 69).

B) The method of Claim 69 comprising the additional limitations of Claims 70-76.

C) A method for obtaining a dendritic cell capable of tolerizing a T-cell for an antigen, the method comprising:

contacting a dendritic cell with dexamethasone *in vitro*; activating the dendritic cell through the CD40 receptor;

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and

contacting the dendritic cell with an antigen, thereby loading the dendritic cell with the antigen, and forming a dendritic cell capable of tolerizing a T-cell for the antigen (Claim 77).

D) The method of Claim 77 comprising the additional limitation of Claims 78-81.

E) The methods of Claims 43 and 75 comprising incubating DCs with a peptide antigen.

F) The method of Claim 53 comprising providing a precursor of a DC.

G) The method of Claim 58 comprising loading DCs with an antigen defined by the response of a T cell.

H) The method of Claims 61, 65, 68, 78, 80, and 81 comprising DCs derived from a graft or transplant donor.

Applicant indicates that support for Claims 69-74 can be found in Claims 40, 41, 49, and 50. Said claims are not originally filed claims and, thus, cannot be cited as support from the specification or claims as filed. Further support for independent Claim 69 is asserted to be found in paragraphs 18, 21, and 23. Applicant indicates that support for Claims 75-80 can be found in Claims 52, 54, 57, 61-63, and 68. Again, said claims are not originally filed claims and, thus, cannot be cited as support from the specification or claims as filed. Further support is asserted to be found in paragraphs 5 and 21-23

A review of the specification shows no support for the specific order of the steps in Claim 69, e.g., contacting the cells with antigen before contacting the DCs with Dex before activating the DCs. Nor does the specification support the specific order of the steps in Claim 77, e.g., contacting the cells with Dex before activating the DCs before contacting the DCs with antigen.

Regarding E), the specification does not disclose peptide antigens and original Claim 9 discloses only synthetic peptides.

Regarding F), the specification does not disclose "a precursor of a DC".

Regarding G), the specification does not disclose "an antigen defined by the response of a T cell".

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Regarding H), the specification does not disclose "DCs derived from a graft or transplant donor".

10. No claim is allowed.

11. The references on the IDS submitted 4/27/05 have been lined through and have not been considered because they have been improperly or incompletely cited. Applicant argues that the references have been cited in accordance with "The [Harvard] Bluebook". Applicant is advised that references must be cited as set forth in the MPEP, see MPEP 609.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

  
1/24/05

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